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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,672	12/09/2003	Shulamit Levenberg	0492611-0530/MIT-10077	6356

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	10/731,672	LEVENBERG ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-11,13-19,22-25,27-34,36-44,47-50,59-71,73 and 75-79* is/are pending in the application.

4a) Of the above claim(s) *59-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-11,13-19,22-25,27-34,36-44,47-50,71,73 and 75-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 59-71, 73, 75-79 are pending. Claims 6, 12, 20-21, 26, 35, 45-46, 51-58, 72 and 74 are canceled. Claims 59-70, are withdrawn. Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 71, 73 and 75-79 are under consideration.

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Claim Rejections - 35 USC § 103/Necessitated by Amendment

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 71 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wobus et al, (J Mol Cell Cardiol, 29: 1525-1539, 1997); in view of Itskovitz-Eldor et al (Molecular Medicine, 6(2): 88-95, 2000); matrix Badylak (US 2003/0216812); Mooney et al, (Biomaterials, 17: 115-124, 1996); Schuldiner et al [PNAS, 97(21): 1107-11312, 2000 (IDS)] is withdrawn necessitated by amendment.

Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, and 75-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Sherwood et al** (Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002) in view of **Griffith et al,** (Science, 295: 1009-1014, 2002 (IDS)).

Sherwood et al teaches a tissue engineering construct, comprising a porous three-dimensional cell support matrix is resistant to contractile forces exerted by chondrocytes such that a cross-sectional area of the matrix scaffolds composed of crystalline L-PLA with an inherent viscosity (I.V.) of 1.1 dl/g and 75% or 90% NaCl shrank less than 2% (abstract, p 4747, 1st column 1st paragraph and throughout the whole document) (claims 1, 4-5, 7-11, 14-15, 22-23, 27-34, 38, 48). Sherwood teaches a large pore size was used (>125 mm) in the bone region to further facilitate mineralized bone ingrowth and mechanical strength (P 4744, 2nd column paragraph) **(claim 75).** Sherwood teaches the polymer of the cell support matrix comprises a 50/50 mixture of poly(L-lactic acid) and poly(Lactic acid-co-glycolic acid) (p 4744 Table 1) **(claims 5, 34).** Sherwood suggests there is a recognized and urgent need for improved treatment of articular cartilage defects (Abstract). Tissue engineering of cartilage using a cell-scaffold approach has demonstrated potential to offer an alternative and effective method for treating articular defects. Sherwood teaches a unique, heterogeneous, osteochondral scaffold using the TheriForm™ three-dimensional printing process and chondrocytes preferentially attached to the cartilage portion of the device, and biochemical and histological analyses showed that cartilage formed during a 6-week in vitro culture period. The tensile strength of the bone region was similar in magnitude to fresh cancellous human bone, suggesting that these scaffolds have desirable mechanical properties for in vivo applications, including full joint replacement (abstract). Sherwood differs from the present invention for not teaching embryonic stem (ES) cells and a cell adhesion promoter and a growth factor to promote the differentiation of ES cells to form tissue-like structures.

However at the time of the instant invention **Griffith et al,** (Science, 295: 1009-1014, 2002 (IDS)) suggest embryonic stem cells hold great promise for treating damaged tissue where the source of cells for repair is extremely limited or not readily accessible (p 1010, 1st column

last paragraph). Griffith et al, suggest embryonic stem cells are attractive because they can be expanded in an undifferentiated state in vitro and can be induced to form many different cell types (p 1010, 1st column and 2nd column). Griffith teaches porous three-dimensional scaffolds that are suitable for growing composite tissue structures such as bone comprising a complete compendium of growth factors and their correctly presented adhesion sites is the next step in tissue engineering (p 1012, 3rd column, 2nd paragraph and figure 1) **(claims 13, 36).** Griffith teaches that tissue engineering is used to restore, maintain, or enhance tissues and organs and engineered tissues could reduce the need for organ replacement, and could greatly accelerate the development of new drugs that may cure patients, eliminating the need for organ transplants altogether (abstract). Griffith et al, also teaches that there are three principal therapeutic strategies for treating diseased or injured tissues in patients: (i) implantation of freshly isolated cells or cultured cells (ii) implantation of tissues assembled in vitro from cells and scaffolds and (iii) in situ tissue regeneration (p 1009, 2nd and 3rd column). Griffith et al, also teaches the three dimensional cell support matrix for in vivo bone scaffolds coated with adhesion proteins such as fibronectin and other extracellular matrix glycoproteins in order to promote maximal tissue in growth (p 1012, 2nd column). Griffith teaches that scaffolds are porous, degradable structures fabricated from either natural materials (collagen, fibrin) or synthetic polymers (polyglycolide, polylactide, polylactide coglycolide); are spongelike sheets, gels, or highly complex structures with intricate pores and channels fabricated using new materials-processing technologies and virtually all scaffolds used in tissue engineering are intended to degrade slowly after implantation in the patient and be replaced by new tissue (p 1010 3rd column, 3rd paragraph) **(claims 14-19, 37).**

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459

(1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Sherwood to utilizing ES-cell instead of chonrocytes, such as ES cells that taught by Griffith et al in a porous scaffold comprising the three dimensional cell support matrix for in vivo bone scaffolds coated with adhesion proteins such as fibronectin and other extracellular matrix glycoproteins in order to promote maximal tissue in growth, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification to use ES cells in order to produce an unlimited source of donor cells for treating damaged tissue where the source of cells for repair is extremely limited or not readily accessible (such as suggested by Griffith), see (p 1010, 1st column last paragraph). This is further underscored by the teachings of Sherwood that scaffold using the TheriForm™ three-

dimensional printing process showed that cartilage formed during a 6-week in vitro culture period the tensile strength of the bone region was similar in magnitude to fresh cancellous human bone, suggesting that these scaffolds have desirable mechanical properties for in vivo applications, including full joint replacement (abstract).

Regarding the various percentages as claimed in claims 7-11, and 27-32 and that a gel coats internal and external surfaces of the cell support matrix in claims 17-19 the MPEP states that "A. Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S.

975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 71, 73 and 75-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Sherwood et al** (Biomaterials, 23: 4739–4751, 2002, Available online 10 September 2002) in view of **Griffith et al,** (Science, 295: 1009-1014, 2002 (IDS)) and further in view of **Benvenisty et al,** (US 2002/0146678 (IDS)).

The teachings of Sherwood and Griffith are applied here as indicated above.

Sherwood and Griffith do not teach the tissue engineered construct comprising activin-A and insulin growth factor (IGF).

However, at the time the claimed invention was made, **Benvenisty et al,** teach methods for mapping a pathway of differentiation of a population of embryonic stem cells which includes exposing the cells to Activin A and wherein cells differentiated into muscle-like syncytium (page 7, 2nd column, example 2). Benvenisty et al, reports while human embryonic stem cells have been recovered from human embryos produced by in vitro fertilization, the formation of embryoid bodies from human primates and from humans has been problematic and the formation of embryoid bodies from primates is inconsistent and asynchronous (p 1, 1st column). Benvenisty et al, have also suggested it is desirable to have tools to analyze and compare pathways indifferent mammals and to combine those these tools with a methodology that permits the isolation, preservation and cultivation of embryonic stem cells from mammals for transplantation in numerous human pathologies as a component in biomedical engineering (p 1 columns 1-2).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Sherwood/Griffith to utilizing ES-cell instead of chonrocytes, such as ES cells that taught by Griffith et al in a porous scaffold comprising the three dimensional cell support matrix for in vivo bone scaffolds coated with adhesion proteins and activin-A with IGF as growth factors as taught by Benvenisty, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to make this modification since Benvenisty provides sufficient rational for one of ordinary skill in the art to apply the three-dimensional cell support system of Sherwood exposing the cells to activin A, wherein using human embryonic stem cells to analyze

and compare pathways indifferent mammals and to combine those tools with a methodology that permits the isolation, preservation and cultivation of embryonic stem cells from mammals for transplantation in numerous human pathologies as a component in biomedical engineering.

Thus, the claimed invention as a whole is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization

where this application or proceeding is assigned is (703) 872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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